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The role of oncoplastic breast conserving treatment for locally advanced breast tumors. A matching case-control study

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HIGHLIGHTS

- A matched case-control study evaluates oncoplastic techniques for locally advanced breast cancer.
- The size of tumors were bigger than other series.
- The matched case-control study was selected base on tumor size and year of diagnosis to decrease possible bias selection.
- The security of this procedure was evaluated based a long follow up.
- Oncoplastic surgery has the same results than conventional breast conserving surgery for locally advanced breast tumors.

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ABSTRACT

Background: Breast conserving surgery (BCS) after neoadjuvant chemotherapy (NC) in patients with locally advanced breast cancer (LABC) is an infrequent procedure. In these patients the association with BCS and oncoplastic surgery (OS) is reported as a possible procedure in case-series, but there are limited case-control studies.

Methods: A matched case-control study evaluated LABC submitted to NC and BCS. We evaluated 78 patients submitted to doxorubicin-cyclophosphamide regimen followed by paclitaxel regimen. The match case-control proportion was 2:1 and the patients were selected by tumor size, clinical T stage and year of diagnosis.

Results: 52 underwent classic BCS and 26 OS. The average size tumor was 5.25 cm and 88.5% of the tumors were larger than 3 cm. The clinical and pathological group characteristics were similar, except the weight of surgical specimens ($p = 0.004$), and surgical margins ($p = 0.06$), which were higher in OS group. The rate of complete pathologic response was 26.9%. 97.4% received postoperative radiotherapy. At 67.1 months of follow up, 10.2% had local recurrence (LR) and 12.8% locoregional recurrence (LRR) and 19.2% died because disease progression. The overall survival at 60 months was 81.7%. After surgery the disease free-survival at 60 months was 76.5%. The was no difference between groups related to pathologic response ($p = 0.42$), LR ($p = 0.71$), LRR ($p = 1.00$), overall survival ($p = 0.99$) and disease specific survival ($p = 0.87$).

Conclusion: This study corroborates the fact that OS is a safety procedure for LABC, offering the similar oncologic results observed in patients submitted to classic BCS.

1. Background

Breast-conserving surgery (BCS) [1,2] was initially indicated for tumors up to 2 or 4 cm but is now used when the tumor/breast

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volume ratio is favorable [3]. The use of radiotherapy made BCS a safe procedure [1,2]. Quality of life and cosmesis have become important points to be considered to improve results [4] and oncoplastic surgery (OS) arises this context [4–6]. OS includes resection of more breast tissue, ease in obtaining safe margins and better cosmetic effect [3–5,7–9], but there is limited evaluation of the long-term effects, whether in terms of recurrence, cosmesis or quality of life [4–6,10–12].

When evaluating BCS in patients undergoing neoadjuvant chemotherapy (NCT) [13], we observed that it is feasible [14] and safe [15,16]. Various factors are involved in its indication, with only a subset of 37–82% [17,18] of patients undergoing this treatment; of these patients, only 1.7%–28% have locally advanced breast cancer (LABC) [18,19]. OS technique [20,21] increase the indications of BCS [11,18].

Case-control studies evaluating OS are limited and based on retrospective analyses [6,11,12,22]. They reported patients with and without NCT [6,11,22–24], but NCT was not the main endpoint. OS depends on the surgeon's training, the tumor's characteristics and the patient's wishes. Likewise, OS involves various procedures at different levels of complexity that come together under the title of OS, a fact that limits prospective studies. The literature reporting the use of OS techniques in the BCS of patients exclusively in undergoing NCT is limited [20]. But, conducting a matched case-control study that exclusively evaluates the role of OS in patients undergoing BCS and NCT is an interesting proposal, and it was this fact that motivated us to conduct this study.

2. Materials and methods

This retrospective sequential case-control study evaluated patients with clinical non-metastatic, non-inflammatory, untreated LABC, treated in a Tertiary Oncological Hospital, from 10/2005 to 12/2011, and who underwent NCT and BCS. During this period, 486 patients underwent NCT, 98 BCS, and 26 BCS combined with oncoplastic breast surgery. A convenience study was performed, but the cases were matched to decrease a possible bias selection. The patients undergoing OS were considered to be cases. The control group of patients undergoing classic BCS was chosen at a ratio 1: 2, where patients were selected based on tumor size, accepting a standard deviation of 5 mm, followed by T clinical staging and the year of the initiation of treatment. The final sample consisted of 52 control patients and a total of 78 patients for analysis.

In this period, the standard neoadjuvant regimen was 4 AC cycles (doxorubicin 60 mg/m [2] + Cyclophosphamide 600 mg/m [2]), followed by 4 T cycles (Taxol [paclitaxel] 175 mg/m^2). At the end, the 4AC + 4T regimen was performed in 83.3% of cases, 4AC + 12T in 10.2% and other regimens in 6.4%, depending on disease progression or treatment toxicity.

The patients were selected from a clinical and radiological point of view before and after NCT. Intraoperative frozen-section examination was available during surgery in all cases. Standard surgical treatment was quadrantectomy combined with level III axillary node dissection with was performed in 97.4% of patients.

All patients were evaluated postoperatively by a multidisciplinary team. 97.4% of patients undergo breast adjuvant radiotherapy (5.040 cGy) associated with tumor bed boost (1.000 cGy) and 85.9% received radiation therapy of the supraclavicular fossa. Patients with estrogen receptor/progesterone receptor (ER/PR)-positive tumors received hormone therapy. Adjuvant chemotherapy was not performed on every patient; it was only used in a palliative manner where there was disease recurrence. Only two patients received adjuvant trastuzumab.

Total follow-up was considered to be the time between the first and last visits. The disease-free interval was considered to be the time between quadrantectomy and either recurrence or last follow-up date. The response to chemotherapy, local recurrence (LR), locoregional recurrence (LRR), and survival were evaluated. Local recurrence was defined as breast recurrence, even if secondary to local infiltration. LRR was defined as local recurrence associated with regional lymph node disease.

The TNM clinical status was used (7th edition, 2010). The slides were reviewed by pathologists (CSN, MM). Where bilateral tumors were present, the one with the highest stage was considered. To evaluate pathologic response we used Chen et al. [16] and NSABP classifications. Complete pathological response was defined as an absence of invasive disease in the breast and axilla. Molecular subtype was evaluated based on an immunohistochemistry technique [25].

2.1. Statistical analysis

Data were collected were tabulated and analyzed using SPSS 20.0 software for Mac®. Initially, the frequencies of categorical variables and the means and standard deviations of continuous variables were analyzed. To compare group characteristics, the chi-square test was used for categorical variables, and Fisher's exact test was used when there were fewer than five patients. The Student's t or Mann-Whitney test was used to compare continuous variables. The Kaplan-Meier method was used for analysis of the risk of disease-free recurrence and overall and specific survival, and the log-rank method was used for the evaluation of differences between groups. The level of statistical significance used was $p < 0.05$.

3. Results

This matched case-control study evaluated patients with LABC who underwent NCT and BCS, where 26 underwent OS (Table 1) and 52 underwent classic quadrantectomy.

The average age of patients was 48.8 years (range 21.3–75.1 years) and the average tumor size was 5.25 cm (range 2.0–8.5 cm). 69.2% of the women had low education levels, 51.3% of the tumors were on the right side, 89.7% of the tumors were clinical stage III, 78.2% tumors were clinical stage T3 and T4, 82.1% of patients had lymph node metastasis, 91.0% of tumors were invasive ductal carcinomas, 94.7% of tumors were Nottingham histologic grade 2/3, 92.1% were nuclear grade 2/3, 61.5% were ER-positive, 52.6% were PR-positive and 23.1% were Her2-positive. Table 2 compares the groups regarding pre-treatment clinical and pathological characteristics, and it should be noted that group stratification revealed no differences between groups.

The breast oncoplastic surgical procedures used were central quadrantectomy (n = 8), dermoglandular rotation flap (n = 7), periareolar quadrantectomy (n = 5), inferior pedicle (n = 4) and superior pedicle (n = 2). All patients in the control group (n = 52) underwent classic quadrantectomy. Contralateral surgery was performed in 12.8% of cases due to benign changes or for obtaining symmetrization (10.3%) or due to the presence of a synchronous contralateral tumor (2.6%). The margins were free in all patients, with a mean of 13 mm (range 1–40 mm), and they were smaller than 2 mm in only three patients (3.9%).

Analysis of post-chemotherapy treatment characteristics revealed that the average weight of the surgical specimen was 241 g (range 41.5–980.0 g), and the mean follow-up time was 63.3 months (range 13.4–105.7 months). Table 3 compares the groups regarding post-treatment clinical and pathological characteristics. In the group stratification, it can be observed that the weight of the surgical specimens of patients undergoing OS was higher ($p = 0.04$) and that the margins were higher in this group, although not